Exhibit E

Exhibit D

Nov. 3, 2015
Letter to FDA

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November 3, 2015

Robert M. Califf, MD, Deputy Commissioner for Medical Products and Tobacco
Janet Woodcock, MD, Director of the Center for Drug Evaluation and Research
Food and Drug Administration
10902 New Hampshire Avenue
Silver Spring, MD 20993

Dear Drs. Califf and Woodcock,

The US Food and Drug Administration approved mifepristone for use in medical abortions on September 28, 2000. Now, 15 years and over 2.5 million uses later, the safety and effectiveness of the drug have been well established by both research and experience, and serious complications have proven to be extremely rare.[1]

We the undersigned are researchers and providers of medical abortion. The organizations we represent include many of the practitioners of medical abortion in the United States. We are writing to present evidence demonstrating that some of the restrictions placed on mifepristone at its initial approval are no longer necessary for the safe and effective use of the drug. We encourage you to exercise your authority to change the label in order to improve both the use of the drug for medical abortion and access to it for this use.

We fully support the following changes to the label:

- The drug should be indicated for use in medical abortions beyond 49 days of gestation.
- The recommended dose regimen should be mifepristone 200 mg followed 24-48 hours later by misoprostol 800 mcg administered buccally.
- The location where the patient should take these drugs should not be restricted.
- An in-person visit should not be mandated for follow-up assessment.
- Any licensed healthcare provider – not just physicians – should be able to prescribe the drug.

All of these provisions are supported by overwhelming evidence and experience, and they reflect current practice in the United States. We hope and expect that you will agree.

We would like to focus here on two additional amendments to the current regulation of mifepristone:

A. Elimination or substantial modification of the Risk Evaluation and Mitigation Strategy (REMS), and
B. Extension of the gestational age limit for medical abortion to 70 days.

Below we discuss the rationale for each of these amendments. Because the elimination or modification of the REMS would have the greatest positive impact on the greatest number of women, we address it first.

A. Elimination or modification of the REMS

When the FDA first approved mifepristone in 2000, experience with its use in non-research settings was minimal, and the decision to impose specific conditions to minimize risk to users was therefore understandable. But over the past 15 years, the safety of the drug has been well established by both research and experience, and serious complications have proven to be extremely rare.[1] Thus, reassessment of the REMS and the Elements To Assure Safe Use (ETASU) which are included in the

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current REMS is warranted. In our judgement, and based on scientific research and our collective experience, the ETASU are no longer justifiable.

As directed by Congress, the FDA may impose ETASU only when needed for the safe administration of the drug (Section 505-1 of the Federal Food, Drug, and Cosmetic Act). Under the law, the ETASU should be reassessed if they are unduly burdensome to the patient, such as when they impede access to health care by patients, including patients in rural or medically underserved areas (FDCA section 505-1(f)(2)(C)(II)). The ETASU requirements must be commensurate with the specific risks listed in the drug labeling, cannot be unduly burdensome on patient access to the drug, must conform with other components for other drugs with similar serious risks, and must be designed to be compatible with established distribution, procurement, and dispensing systems for drugs (FDCA section 355-1(f)(2)).

Below we review the specific components of the ETASU for mifepristone (Mifeprex) and provide our recommendations for modifying them.

1. Dispensing venues. The ETASU currently require that mifepristone must be dispensed to patients in a clinic, medical office, or hospital. This requirement meets none of the ETASU principles described above.

   - The requirement has no relation to the serious risks described in the "black box warning" on the mifepristone label which are "serious and sometimes fatal infections and bleeding". If these conditions occur, which the label notes happens "very rarely", they begin hours after the drug is ingested and thus cannot possibly be mitigated by requiring that the drug be dispensed in any specific venue. The same is true for all other adverse events listed on the mifepristone label. Notably, the ETASU does not specify that the drug must be ingested in the medical facility, only that it must be dispensed there. In fact, recent research has shown that allowing each patient to ingest the mifepristone in the place and time of her choosing is safe, desirable, and highly acceptable to women who choose the option.[2-4] This research further supports the conclusion that the location where the drug is dispensed has no bearing on risk.
   - The requirement creates a burden to access by necessitating that each providing facility must order supplies of the drug in advance of need, properly store these supplies, and maintain inventory records according to applicable pharmacy laws. These procedures are both financially and logistically onerous, particularly for small facilities. Anecdotal reports suggest that the burden is significant enough to dissuade some providers from offering the service to patients.
   - The requirement is not commensurate with the requirements for distribution of other drugs, including drugs that are much more immediately dangerous than mifepristone. For example, antibiotics, anti-hypertensives, erectile dysfunction drugs, and insulin have been reported to cause serious or fatal reactions shortly after use, yet are all distributed in pharmacies. Furthermore, since each medical abortion patient receives only a sufficient amount of mifepristone for her own abortion, risks such as overdose or redistribution that may be of concern for drugs that are dispensed in pharmacies in multiple doses are not salient for mifepristone. Moreover, mifepristone under the brand name Korlym is mailed by a specialty pharmacy directly to patients with Cushing's syndrome and is taken at home.

   Abortion providers certainly can safely evaluate patients and prescribe mifepristone without having the tablets physically present in their offices. We therefore recommend that this requirement be removed entirely and that mifepristone should be available in retail pharmacies like other prescription drugs.

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2. Provider certification. The ETASU require that to prescribe mifepristone, a provider must obtain certification by submitting a form attesting that he or she:
   - is able to assess the duration of pregnancy accurately;
   - is able to diagnose ectopic pregnancies;
   - is able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or has made plans to provide such care through others, and is able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary; and
   - has read and understood the prescribing information.

   Fulfilling these criteria requires no specialized medical expertise. Although many clinicians use history and/or clinical examination to assess the duration and location of a pregnancy, any provider who is not comfortable with these approaches can order an ultrasound. Similarly, any provider can appropriately plan to provide care for emergencies by referring patients to an emergency room if needed. No licensed healthcare professional would be unable to read or understand the prescribing information. A standard clinical license should be sufficient to assure that a provider meets these qualifications; an exceptional certification for mifepristone is unnecessary.

   Provider certification for mifepristone is also inconsistent with the requirements for prescribing other drugs that require careful patient screening to ensure safety. For example, clinicians are not required to certify their ability to diagnose heart disease before prescribing powerful cardiovascular drugs, to diagnose infections before prescribing antibiotics, or to assess schizophrenia before prescribing antipsychotics. Evaluating a patient for each of these conditions is much more complicated than assessing the duration or location of a pregnancy. Singling out mifepristone for certification is inappropriate.

   Furthermore, the certification process inhibits access to mifepristone. Most immediately, because the certification process must be completed in advance of the patient encounter, it prevents qualified clinicians who have not completed the certification from providing the service to patients who present for care unexpectedly. More broadly, the process of obtaining certification may discourage some providers from offering the service to any patients. Given the history of harassment and violence against abortion providers in this country and the demonstrated difficulty in maintaining confidentiality in the current environment, some clinicians are understandably reluctant to allow their names to be included in a list of abortion providers.

   Finally, the certification requirement should be eliminated because it would be incompatible with standard distribution of mifepristone in pharmacies. Setting up and maintaining a system whereby pharmacies could check the certification status of prescribers would be impractical.

3. Patient Agreement. The requirement that each patient should sign an FDA-approved agreement before receiving mifepristone should also be eliminated. Like the other parts of the ETASU, this requirement is inconsistent with requirements for other drugs with similar or greater risks. Medical abortion is a treatment, not a procedure, and it is highly unusual to require patients to sign agreements for other safe treatments – for example, treatment of a sexually transmitted infection, or a nebulizer treatment for asthma. In addition, in places where off-label use of mifepristone is permitted, the content of any FDA-approved agreement may be inconsistent with the care provided by the individual clinician. The requirement that a patient sign an agreement to a treatment plan that differs from the one offered by her provider is both inappropriate and confusing.

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Making these changes to the ETASU would render other parts of the REMS obsolete. For example, the distributor certification, as currently written, would become unnecessary if provider certification were not required and pharmacy distribution were permitted. If the ETASU elements are eliminated, the REMS Assessments are no longer needed either. We recommend that the REMS should be discontinued in its entirety, consistent with the FDA's current efforts to decrease disruption to the healthcare system caused when some drugs are subject to distribution requirements that differ from the norm.

The immense volume of data about and experience with mifepristone since its initial approval have demonstrated that this drug is extremely safe and can be appropriately provided by clinicians with routine professional training. Standard professional labeling is clearly sufficient to ensure that its benefits outweigh its risks.

B. Extension of the gestational age limit to 70 days

Substantial evidence demonstrates that the proposed medical abortion regimen is highly effective in the 10th week (64-70 days) of gestation (defined as days since onset of the last menstrual period or estimated days since ovulation + 14). A recent systematic review identified four published prospective studies that recorded data on outcomes of medical abortions performed during this 10th week.[5] We have subsequently found two additional published studies,[6,7] and Gynuity Health Projects recently has conducted two additional studies that are not yet published that also include such data. The published studies were conducted in the United States,[8] Mexico,[9,10] Curaçao,[11] Vietnam,[6,7] and the Republic of Georgia,[7] and the two unpublished studies were conducted in the United States and Mexico. All subjects were treated as outpatients between 2007 and 2015.

The eight studies included a combined total of 634 women treated at 64-70 days of gestation, of whom 587 (91%) provided outcome data (Table 1). Of these women, 92.4% (95% CI 89.9%, 94.4%) had complete medical abortion success (pregnancy termination without resort to surgical intervention), and 3.1% (95% CI 1.9%, 4.9%) had ongoing pregnancies (Table 1). These proportions were not clinically or statistically different from the results obtained in women treated in the 9th gestational week (57-63 days) in the same studies (Table 2). Perhaps more importantly, the complete abortion success rate was comparable to the standard set by the FDA for medical abortion effectiveness in its initial approval of mifepristone in 2000; the proportion of subjects with complete abortion success in the US pivotal trial that supported that approval was 92.1%.[12]

Data from the eight studies also document that medical abortion in the 10th gestational week is safe. Only 7 of the 578 subjects (1.2%, 95%CI 0.5%, 2.5%) treated in that week had serious adverse events, a proportion nearly identical to that among subjects treated in the 9th gestational week (11/1010, 1.1%, 95%CI 0.5%, 1.9%). Two of the studies found that women treated at 64-70 days experienced more side effects, such as vomiting, diarrhea, and weakness, than women treated in the prior week, but these events were managed on an outpatient basis and were self-limited.[8,9] The same two studies also reported data on satisfaction; in these studies, more than 75% of the women treated in the 10th week noted that their medical abortion was satisfactory or would choose it over surgical abortion for a future abortion.

Based on these published and well-known data, medical abortion practice in the United States is rapidly expanding to include provision of the service through 70 days of gestation. The National Abortion Federation updated its Clinical Practice Guidelines in 2013 to recommend the 70-day gestational age limit, and in 2015, 55% of respondents to the annual NAF member survey reported providing medical abortion up to 70 days (Vicki Saporta, President, NAF, personal communication June 10, 2015). Similarly,

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over the past several years, about half of Planned Parenthood affiliates have indicated their intentions to offer services to women up to 70 days, and have provided services to hundreds of women at 64-70 days of gestation (Deborah VanDerhei, National Director, CAPS, Planned Parenthood Federation of America, personal communication June 10, 2015).

Considering the current evidence, we submit that medical abortion is safe and effective through at least 70 days since last menstrual period (LMP) and that a label specifying a maximum gestational age less than that is unnecessarily and arbitrarily conservative. Women who present for abortion in the 10th gestational week currently constitute about 7% of all abortion patients nationally.[13] This is a significant proportion and limitations to access to medical abortion would have significant negative consequences for those women.

Although off-label use of drugs is generally accepted in the United States, many clinicians see FDA labels as guides to appropriate and legally defensible clinical practice. A gestational limit lower than 70 days on the mifepristone label may discourage some clinicians from offering medical abortion to this subgroup of patients. In addition, in states where off-label use of mifepristone is prohibited by law, women at a later gestational age would be entirely prevented from accessing medical abortion. Because of these state laws demanding strict compliance with the label, it is important for the FDA to include on the label all situations where medical abortion is safe and effective. And as a growing number of non-hospital abortion providers offer medical abortion but not surgical abortion,[14,15] these women will need to travel farther and at greater cost to access abortion services at all.

The data presented here are sufficient to establish the efficacy and safety of outpatient medical abortion with mifepristone and misoprostol through 70 days LMP. Including this information on the mifepristone label would be consistent with the FDA's mission to promote public health through the effective and safe use of drugs. Furthermore additional studies of outpatient medical abortion through 70 days LMP are ongoing and we would be happy to forward more information as it becomes available.

We would be happy to provide further details regarding the data we have presented. We appreciate your consideration of the requests that we have made in this letter.

Respectfully yours,

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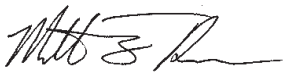

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